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PATENT

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

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| APPLICANT(S)              | : | Cleveland State University              |
| INTERNATIONAL APP. NO.    | : | PCT/US04/21487                          |
| INTERNATIONAL FILING DATE | : | July 1, 2004                            |
| TITLE                     | : | EXOSITE-DIRECTED THROMBIN<br>INHIBITORS |
| OFFICER                   | : | Sandra E. Saucier                       |
| ATTORNEY DOCKET NO.       | : | CLEV 2 00023 PCT                        |

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REPLY TO INTERNATIONAL SEARCH REPORT AND  
WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY

MAIL STOP PCT  
Commissioner for Patents  
P.O. Box 1450  
Alexandria, VA 22313-1450  
ATTN.: RO/US

Dear Sir:

This is in reply to the International Search Report and Written Opinion of the International Searching Authority, both mailed on July 18, 2005 in the above-captioned patent application.

The International Searching Authority searched the art relating to claims 1-8, 10, 43-49, and 51 in the present patent application. Claims 2-5 were indicated as meeting the requirements for novelty, inventive step, and industrial applicability.

In the International Search Report, two documents, one to Hortin and one to Beck et al., were cited and designated as "X" documents. None of the other documents, which were all designated as "A" category documents (indicating general state of the art) are believed to be relevant to the pending claims. For the reasons set forth below, it is respectfully submitted that neither document designated as an "X" document, is relevant to the patentability of the remaining claims at issue, namely claims 1, 6-8, 10, 43-49, and 51.

**A. Hortin Article is Readily Distinguishable From the Pending Claims**

As described in the specification of the present application, the present invention relates to the discovery of specific peptides, typically of four or five amino acids, that have been found to significantly inhibit the generation of thrombin and thus serve as anticoagulants. These particular peptides include those containing the amino acid sequence DYDY, DYDYQ, and the sulfonated sequences of DYDY and DYDYQ, in which at least one of the Y amino acids is sulfonated.

The article by Hortin<sup>1</sup> merely describes several fragments of the human coagulation factor V. One of the fragments is the well known factor Va. Hortin speculates a region of the fragment Va, using a predictive algorithm, as depicted in Figure 6.

Hortin entirely fails to identify any specific sequence of amino acids in any region of factor Va that are responsible for inhibiting the generation of thrombin. Furthermore, Hortin entirely fails to disclose that if any particular peptide or sequence of amino acids from any region of factor Va were isolated, that the peptide or amino acid sequence would exhibit the anticoagulant effects of the present invention.

For at least this reason, it is respectfully submitted that the article to Hortin is not relevant to any of claims 1, 6-8, 10, 43-49, and 51.

Furthermore, each of claims 1, 6-8, 10, 43-49 and 51 recites, in part, a particular peptide. Claims 1 and 6-8 recite the peptide itself. Claim 10 recites a peptide analogue that mimics the peptide of claim 1. Claims 43-49 call for a pharmaceutical composition that comprises a particular peptide. And, claim 51 recites a pharmaceutical composition that comprises a peptide analogue that mimics the peptide of claim 43.

In regard to the Hortin article, it was asserted in the Written Opinion that claim 1 is "interpreted as being broadly drawn to any peptide having the sequence DYDY, which includes factor Va itself."<sup>2</sup>

It is respectfully submitted that an overly broad interpretation is being given to the term "peptide" in the claims at issue. The term "peptide" generally refers to a

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<sup>1</sup> Hortin, G.L., "Sulfation of Tyrosine Residues in Coagulation Factor V," Blood, 1 September 1990, Vol. 76, No. 5, pages 946-952.

<sup>2</sup> See item 2, Citations and explanations of Box No. V of the Written Opinion.

relatively short chain of amino acids, such as from about 2 to about 10 amino acids, and at most up to about 50 amino acids.<sup>3</sup>

In contrast, factor Va as disclosed in the Hortin article is a protein, and includes about 1800 amino acids. Practitioners in the field of biochemistry refer to factor Va as a protein or fragment of a larger protein, factor V. Restated, factor Va would not be considered a peptide, and so is excluded by each of the claims at issue, i.e., claims 1, 6-8, 10, 43-49, and 51, since each of those claims expressly recites a "peptide".

For at least these reasons, it is respectfully submitted that claims 1, 6-8, 10, 43-49, and 51 are readily distinguishable from the article to Hortin.

#### **B. Beck et al. Article is Not Prior Art to the Pending Claims**

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Peptides differ from proteins, which are also long chains of amino acids, by virtue of their size. Traditionally, those peptide chains that are short enough to make synthetically from the constituent amino acids are called peptides rather than proteins. The informal dividing line is at approximately 50 amino acids in length.

[www.answers.com/topic/peptide](http://www.answers.com/topic/peptide), p. 2

Biochemical formed by the linkage of up to about 50 amino acids to form a chain. Longer chains are called proteins.

[www.thebody.com/hivatis/glossary/p.html](http://www.thebody.com/hivatis/glossary/p.html)

A short polymer (~2-10 units) of amino acids.

[www.visionlearning.com/library/pop-glossary-term.php](http://www.visionlearning.com/library/pop-glossary-term.php)

Small peptides with fewer than about ten constituent amino acids are called oligopeptides, and peptides with more than ten amino acids are termed polypeptides. Compounds with molecular weights of more than 10,000 (50-100 amino acids) are usually termed proteins.

[www.answers.com/topic/peptide](http://www.answers.com/topic/peptide)

Peptides differ from proteins, which are also long chains of amino acids, by virtue of their size. Traditionally, those peptide chains that are short enough to make synthetically from the constituent amino acids are called peptides rather than proteins. The dividing line is at approximately 50 amino acids in length, since naturally-occurring proteins tend, at their smallest, to be hundreds of residues long.

[www.websters-online-dictionary.org/definition/english/pe/peptide.html](http://www.websters-online-dictionary.org/definition/english/pe/peptide.html)

The present application is based upon, and claims priority upon U.S. Provisional Application Serial No. 60/502,186, filed on September 12, 2003. This is the effective filing date of the present application and predates the publication date of the article to Beck et al., which is October 14, 2003.

For at least this reason, the Beck et al. article is not prior art to any of the pending claims.

**C. Amendments to Claims 6 and 7**

In view of the observations of the International Searching Authority, claims 6 and 7 have been amended to replace the term "exhibits" with the term "comprises".

**D. New Claims 112-135 Are Distinguishable From the Cited Documents**

New claims 112-135 are presented and are directed to specific aspects of the present invention that are believed to be readily distinguishable from the cited documents.

New claims 112-115 correspond to claims 1, 6, 8, and 10, respectively, with the exception that claim 112 recites that the claimed peptide "consists of a sequence of four amino acids . . . ."

Similarly, new claims 116-119 correspond to claims 1, 7, 8, and 10, respectively, with the exception that claim 116 recites that the claimed peptide "consists of a sequence of five amino acids . . . ."

New claims 120-127 correspond to claims 43-49 and 51, respectively, with the exception that claim 120 recites a pharmaceutical composition that comprises a peptide "consisting of" an amino acid sequence DYDY.

And, likewise, new claims 128-135 correspond to claims 43-49 and 51, respectively, with the exception that claim 128 recites a pharmaceutical composition that comprises a peptide "consisting of" an amino acid sequence of DYDYQ.

No new matter is added by any of these claims since support is found throughout the present application.

It is respectfully urged that all of new claims 112-135 are readily distinguishable from the Hortin article. Hortin, as previously explained, entirely fails to disclose any of the specific peptides recited in claims 112-119, or any of the pharmaceutical compositions recited in claims 120-135.

The article to Beck et al. is not prior art to the new claims for the reasons previously expressed.

None of the other articles designated as "A" category documents are believed to be relevant to new claims 112-135.

**E. Clarification of Terms in Claims 10 and 51 (and New Claims 115, 119, 127, and 135)**

In the observations of the International Searching Authority, uncertainty was expressed as to the term "mimics" appearing in claims 10 and 51. That term refers to a characteristic of a compound to mimic the critical features of the molecular recognition process of a peptide of interest and thereby block or reproduce the action of the peptide. Additional description and examples of this term are provided on page 17, lines 7-21 of the present application.

Concern was also expressed as to what class of chemical "analogue" refers. This term also appears in claims 10 and 51. This term refers to "a compound that is capable of mimicking or antagonizing the biological action(s) of a parent or natural peptide." See page 17, lines 7-21 of the present application for further explanation and examples of this term.

It is respectfully submitted that the term "mimics" and "analogue" appearing in claims 10 and 51, and new claims 115, 119, 127, and 135, are sufficiently definite and clear.

**F. Conclusion**

In view of the foregoing explanations and clarifications, it is respectfully submitted that, in addition to claims 2-5, the other claims under review, i.e., claims 1, 6-8, 10, 43-49, and 51, also meet the requirements for novelty and inventive step. Also, it is respectfully submitted that each of new claims 112-135 also meets all requirements for novelty, inventive step, and industrial applicability.

Although no fees are believed due and owing, the Receiving Office is authorized to charge any required fees to Deposit Account No. 06-0308.

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13 MAR 2006

Respectfully submitted,

FAY, SHARPE, FAGAN,  
MINNICH & McKEE, LLP



Mark E. Bandy, Reg. No. 35,788  
1100 Superior Avenue, Seventh Floor  
Cleveland, OH 44114-2579  
216/861-5582

September 16, 2005

Date

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| Printed Name<br>Mary Ann Temesvari     |

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## CLAIMS:

1. A peptide having a sequence of amino acids which is identical to a sequence of consecutive amino acids found within amino acids 695 to 698 (SEQ ID NO. 10) of the human blood clotting factor Va.  
5
2. The peptide of claim 1 wherein the peptide exhibits an  $IC_{50}$  of less than about 100  $\mu M$ , the  $IC_{50}$  being the amount of the peptide that inhibits 50% of the activity of human factor Va.  
10
3. The peptide of claim 2 wherein the peptide exhibits an  $IC_{50}$  of less than about 15  $\mu M$ .
4. The peptide of claim 3 wherein the peptide exhibits an  $IC_{50}$  of about 1.6  $\mu M$ .  
15
5. The peptide of claim 4 wherein the peptide exhibits an  $IC_{50}$  of about 500 nM.
6. The peptide of claim 1 wherein the peptide comprises the amino acid sequence DYDY.  
20
7. The peptide of claim 1 wherein the peptide comprises the amino acid sequence DYDYQ.  
25
8. A pharmaceutical composition comprising the peptide of claim 1.
9. A method for treating human subjects having blood clotting disorders, the method comprising administering the pharmaceutical composition of claim 8 to the human subjects.  
30
10. A peptide analogue that mimics the peptide of claim 1.

107. The method of claim 106 wherein the amino acid sequence is DY(-SO<sub>3</sub>)DY(-SO<sub>3</sub>)Q.

108. The method of claim 102 wherein the effective amount of the peptide is in the range of from about 0.01 to 1000 mg/kg of body weight, per day.

109. The method of claim 108 wherein the effective amount of the peptide is in the range of from about 0.1 to 100 mg/kg of body weight, per day.

110. The method of claim 109 wherein the effective amount of the peptide is in the range of from about 1 to 10 mg/kg of body weight, per day.

111. A method for inhibiting thrombin generation in a patient suffering from a blood coagulation disorder, the method comprising:

administering to the patient an effective amount of a peptide that mimics the peptide of the method of claim 102.

112. A peptide consisting of a sequence of four amino acids which is identical to a sequence of consecutive amino acids found within amino acids 695 to 698 (SEQ ID NO. 10) of the human blood clotting factor Va.

113. The peptide of claim 112 wherein the peptide comprises the amino acid sequence DYDY.

114. A pharmaceutical composition comprising the peptide of claim 112.

115. A peptide analogue that mimics the peptide of claim 112.

116. A peptide consisting of a sequence of five amino acids which is identical to a sequence of consecutive amino acids found within amino acids 695 to 699 (SEQ ID NO. 11) of the human blood clotting factor Va.

117. The peptide of claim 116 wherein the peptide comprises the amino acid sequence DYDYQ.

118. A pharmaceutical composition comprising the peptide of claim 116.

119. A peptide analogue that mimics the peptide of claim 116.

5 120. A pharmaceutical composition adapted for inhibiting thrombin generation, the composition comprising a peptide consisting of an amino acid sequence DYDY (SEQ ID NO. 10).

10 121. The pharmaceutical composition of claim 120 further comprising a carrier.

122. The pharmaceutical composition of claim 120 wherein one of the Y amino acids of the amino acid sequence is sulfonated.

15 123. The pharmaceutical composition of claim 122 wherein the amino acid sequence of the peptide is DY(-SO<sub>3</sub>)DY.

124. The pharmaceutical composition of claim 122 wherein the amino acid sequence of the peptide is DYDY(-SO<sub>3</sub>).

20

125. The pharmaceutical composition of claim 120 wherein both of the Y amino acids of the amino acid sequence are sulfonated.

25 126. The pharmaceutical composition of claim 125 wherein the amino acid sequence of the peptide is DY(-SO<sub>3</sub>)DY(-SO<sub>3</sub>).

127. A pharmaceutical composition comprising a peptide analogue that mimics the peptide of the composition of claim 120.

30 128. A pharmaceutical composition adapted for inhibiting thrombin generation, the composition comprising a peptide consisting of an amino acid sequence DYDYQ (SEQ ID NO. 11).

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129. The pharmaceutical composition of claim 128 further comprising a carrier.

130. The pharmaceutical composition of claim 128 wherein one of the Y  
5 amino acids of the amino acid sequence is sulfonated.

131. The pharmaceutical composition of claim 130 wherein the amino acid sequence of the peptide is DY(-SO<sub>3</sub>)DYQ.

10 132. The pharmaceutical composition of claim 130 wherein the amino acid sequence of the peptide is DYDY(-SO<sub>3</sub>)Q.

133. The pharmaceutical composition of claim 128 wherein both of the Y amino acids of the amino acid sequence are sulfonated.

15

134. The pharmaceutical composition of claim 133 wherein the amino acid sequence of the peptide is DY(-SO<sub>3</sub>)DY(-SO<sub>3</sub>)Q.

135. A pharmaceutical composition comprising a peptide analogue that  
20 mimics the peptide of the composition of claim 128.